Intravenous versus Oral Paracetamol: A Comparative Analysis of Efficacy, Safety, and Clinical Utility

1. Introduction

Paracetamol, also known as acetaminophen, is a cornerstone analgesic and antipyretic agent, extensively utilized worldwide across diverse patient populations and clinical settings. It is available in multiple formulations, including the traditional oral route and, more recently, an intravenous (IV) preparation. While the precise mechanism of action of paracetamol remains a subject of ongoing research, it is understood to primarily involve the inhibition of prostaglandin synthesis within the central nervous system (CNS). Further evidence suggests modulation of the endogenous cannabinoid system via its metabolite N-arachidonoylphenolamine (AM404), which acts on TRPV1 and cannabinoid CB1 receptors, and potential interactions with descending serotonergic pathways contributing to its analgesic effects.

The introduction and approval of an IV formulation of paracetamol (e.g., Ofirmev by the FDA in 2010) has led to significant clinical interest and debate regarding its comparative benefits over the well-established and considerably more economical oral route. This has prompted clinicians and researchers to question whether, and in what specific circumstances, IV paracetamol offers clinically meaningful advantages that justify its increased cost and resource utilization. The long-standing use of oral paracetamol, characterized by a generally favorable safety profile when used appropriately and broad accessibility , establishes a considerable benchmark. For a newer, more expensive formulation like IV paracetamol to be deemed "better" in a general sense, it must demonstrate substantial and clinically relevant improvements in efficacy, safety, or utility that extend beyond mere convenience in specific, limited scenarios.

This report aims to provide a comprehensive and critical evaluation of the available evidence comparing IV and oral paracetamol. The analysis will encompass a detailed examination of their respective pharmacokinetic profiles, clinical efficacy in various settings (including postoperative pain, acute pain in emergency departments, and pediatric use), comparative safety and tolerability, cost-effectiveness, environmental impact, and existing clinical guidelines from professional bodies. The central objective is to determine if, and under what specific clinical conditions, the intravenous route of paracetamol administration offers superior clinical benefit compared to the oral route. It is important to recognize that the term "better" is inherently context-dependent. Therefore, this investigation will seek to dissect whether "better" refers to a faster onset of action, higher peak plasma concentrations, more reliable absorption (particularly in compromised patient groups or with concomitant medications), improved pain scores, reduced incidence of adverse effects, or unique suitability for patients unable to utilize the oral route. A nuanced answer, rather than a generalized pronouncement, is essential for informing clinical decision-making.

2. Pharmacological Profile: A Comparative Analysis

Understanding the pharmacological distinctions between intravenous and oral paracetamol is

fundamental to appreciating their potential differences in clinical performance. Key pharmacokinetic parameters such as bioavailability, rate and extent of absorption, metabolism, and distribution to target sites, including the central nervous system, are critical determinants of a drug's onset, intensity, and duration of action.

2.1. Bioavailability and First-Pass Metabolism

Oral paracetamol is generally well absorbed from the gastrointestinal (GI) tract, although its bioavailability can vary. Estimates range from 63-89% to as high as 85-98% in some reports. Following oral administration, paracetamol undergoes first-pass hepatic metabolism, where a portion of the drug is metabolized in the liver before reaching systemic circulation. This initial pass through the liver means the organ is exposed to a higher concentration of the drug shortly after oral ingestion.

In contrast, intravenous paracetamol administration ensures 100% bioavailability, as the drug is introduced directly into the systemic circulation, thereby bypassing the absorption phase in the GI tract and avoiding first-pass hepatic metabolism. A significant consequence of bypassing first-pass metabolism is that the liver may be exposed to approximately 50% less initial paracetamol following an IV dose compared to an equivalent oral dose.

The avoidance of first-pass metabolism with IV administration presents a theoretical advantage regarding hepatoprotection, particularly when considering dosing at the upper end of the therapeutic range or in patients with pre-existing liver compromise. Since paracetamol's primary toxicity is dose-dependent hepatotoxicity, mediated by its reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), reducing the initial hepatic exposure could, in theory, lessen the burden on metabolic pathways and reduce NAPQI formation. However, the clinical significance of this theoretical benefit at standard therapeutic doses in individuals with normal hepatic function is not definitively established. Reports of hepatotoxicity associated with IV paracetamol are primarily linked to dosing errors rather than an inherent risk at appropriate therapeutic levels. Furthermore, if the overall systemic exposure, as measured by the area under the plasma concentration-time curve (AUC), is similar between the two routes once oral absorption is complete , the long-term impact on liver burden might be less disparate than the initial exposure suggests, unless the rate of NAPQI formation is saturated during the first pass of an oral dose.

The documented variability in oral bioavailability (ranging from 63% to potentially 98%) implies that for some individuals, or under specific physiological or pathological conditions (e.g., altered gastric pH, GI motility disorders, presence of food, drug interactions), oral administration might result in suboptimal or unpredictable systemic exposure compared to the guaranteed and consistent 100% bioavailability achieved with the IV route. This variability can translate into inconsistent plasma concentrations and, consequently, potentially erratic therapeutic effects, a concern particularly relevant in critically ill patients or those with compromised GI function where reliable drug delivery is paramount. IV administration effectively circumvents this absorption variability.

2.2. Key Pharmacokinetic Parameters: Tmax, Cmax, and AUC

The pharmacokinetic profile of a drug is characterized by several key parameters, including the time to reach peak plasma concentration (T_{max}), the peak plasma concentration itself (C_{max}), and the total drug exposure over time (AUC).

- **T_{max} (Time to Peak Plasma Concentration):** For oral paracetamol, T_{max} is

typically observed within 30 to 60 minutes post-administration. However, this can be variable; studies have shown that with a 1g oral dose, some patients did not achieve detectable plasma levels within an 80-minute observation period, whereas a 2g oral dose achieved therapeutic concentrations after approximately 40 minutes. In contrast, IV paracetamol achieves T_{max} much more rapidly, typically at the end of the standard 15-minute infusion period , or within 15 to 20 minutes of administration.

- **C_{max} (Peak Plasma Concentration):** Following IV administration, C_{max} can be up to 70% higher than that achieved with an equivalent oral dose. For instance, a 1g IV dose of paracetamol resulted in a mean C_{max} of 14.4 µg/mL within 20 minutes. Oral administration generally results in a lower and more variable C_{max}.
- **AUC (Area Under the Plasma Concentration-Time Curve):** The AUC, which reflects the overall systemic exposure to the drug, is generally considered to be very similar between IV and oral routes, provided that the oral dose is completely absorbed.

While IV paracetamol clearly achieves a significantly faster T_{max} and a higher C_{max}, the clinical relevance of these pharmacokinetic advantages for paracetamol's overall analgesic efficacy is a subject of debate, particularly if the total drug exposure (AUC) is comparable between the routes. Analgesic effects are often correlated with maintaining drug concentrations within a defined therapeutic window. If oral paracetamol, despite a slower rise to peak and a lower peak concentration, achieves and sustains therapeutic concentrations for a duration similar to IV paracetamol (as suggested by a similar AUC), the net analgesic outcome over several hours might be comparable. This could explain why numerous clinical trials have failed to demonstrate superior pain relief with IV paracetamol despite its more rapid initial absorption profile.

Nevertheless, the rapid attainment of a high C_{max} with IV paracetamol could be particularly advantageous in clinical scenarios characterized by acute, severe pain where immediate onset of analgesia is a primary therapeutic goal. In such situations, the faster T_{max} and higher C_{max} associated with IV administration directly translate to a quicker onset of action , potentially bridging the critical time gap until other analgesics take effect or until oral medication can be administered and absorbed. Even if the overall duration or magnitude of pain relief over an extended period is similar to that of oral paracetamol, this initial speed can represent a significant clinical advantage in urgent care settings.

2.3. Impact of Concomitant Medications (e.g., Morphine) on Paracetamol Pharmacokinetics

A critical factor influencing the choice between oral and IV paracetamol, especially in the postoperative setting, is the effect of co-administered medications, particularly opioids like morphine. Research has demonstrated that morphine co-administration significantly impacts the pharmacokinetics of oral paracetamol. Specifically, morphine can reduce and delay the absorption of oral paracetamol, leading to a decrease in C_{max} (e.g., from 11.6 to 7.25 µg/mL in one study) and AUC (e.g., AUC_{0–6} reduced from 31.00 to 25.51 µg·h/mL), and a prolongation of T_{max}. This interaction can also result in an abrupt release of accumulated paracetamol from the GI tract once the morphine-mediated inhibition of GI motility subsides. Conversely, the pharmacokinetic parameters of IV paracetamol are not affected by the co-administration of morphine. This is because IV administration bypasses the GI tract, making its absorption independent of gastric emptying rates or intestinal motility. Consequently, IV paracetamol provides more predictable and consistent plasma concentrations when

administered concurrently with opioids.
This distinction is of paramount clinical importance, especially in postoperative pain management where opioids are frequently integral to analgesic regimens. The unreliability and potential impairment of oral paracetamol absorption in the presence of opioids strongly argue in favor of IV administration if predictable and consistent analgesia from paracetamol is desired in this context. Opioids are known to delay gastric emptying and reduce GI motility, which directly hinders the absorption of orally administered drugs. IV paracetamol circumvents these issues, ensuring its delivery to the systemic circulation is unaffected by opioid-induced GI changes, thus leading to more reliable therapeutic effects.
Furthermore, the phenomenon described as an "abrupt release of accumulated paracetamol" from the GI tract after the inhibitory effects of morphine diminish raises a potential safety concern with oral paracetamol. If a significant amount of orally administered paracetamol accumulates in the stomach due to opioid-induced GI stasis and is then rapidly absorbed as opioid effects wane, it could lead to an unexpectedly high surge in plasma concentration. This could be problematic if the timing of subsequent scheduled doses of oral paracetamol does not account for this bolus absorption, potentially increasing the risk of exceeding therapeutic concentrations and, theoretically, enhancing the risk of toxicity, particularly with repeated dosing regimens. IV administration avoids this complication of unpredictable GI accumulation and release.

2.4. Distribution: Including Cerebrospinal Fluid (CSF) Concentrations

Paracetamol's analgesic action is believed to be mediated significantly within the CNS. Therefore, the extent and rate of its distribution into the cerebrospinal fluid (CSF) are relevant to its efficacy. Studies have shown that IV administration of paracetamol results in significantly higher mean CSF concentrations compared to oral or rectal formulations. For example, one study comparing 1g doses of paracetamol administered via IV, oral, or rectal routes found the CSF AUC_{0–6} to be 24.9 μg·h/mL, 14.2 μg·h/mL, and 10.3 μg·h/mL, respectively.
Given that paracetamol is thought to inhibit cyclooxygenase (COX) enzymes in the brain and spinal cord and may exert effects via its metabolite AM404 on central cannabinoid CB1 receptors and TRPV1 channels , the higher and more rapid attainment of CSF concentrations following IV administration could theoretically translate into a faster and more pronounced central analgesic effect. Higher drug concentrations at the site of action (i.e., the CNS) would logically be expected to produce a greater or more rapid therapeutic response. The ability of IV paracetamol to achieve higher CSF levels more quickly thus provides a plausible pharmacological basis for a superior or faster onset of central analgesia.
However, despite this pharmacokinetic advantage in CSF penetration, the translation of these higher CSF levels into consistently superior clinical pain relief across broad patient populations is not definitively established by all clinical studies. Many trials report comparable overall pain relief between IV and oral routes when oral absorption is adequate. This discrepancy suggests that either the magnitude of difference in CSF concentrations achieved by optimally absorbed oral versus IV paracetamol may not always cross a critical threshold for differential efficacy in all pain states, or that other factors, such as peripheral analgesic actions of paracetamol or inter-individual variability in response, play a significant role in the overall clinical effect. It is plausible that for many common pain scenarios, the oral route, when effectively absorbed, achieves *sufficient* CSF concentrations to elicit a satisfactory analgesic response.

Table 1: Comparative Pharmacokinetic Parameters of Intravenous vs. Oral Paracetamol

To summarize the key pharmacokinetic distinctions, Table 1 provides a comparative overview:

Parameter	Intravenous (IV) Paracetamol	Oral Paracetamol	Key References
Bioavailability	100%	63-89% (up to 98% in some reports)	
First-Pass Metabolism	Bypassed	Undergoes hepatic first-pass metabolism	
T_{max} (Time to Peak)	End of 15-min infusion; ~15-20 mins	30-60 mins (variable; can be >80 mins for 1g, ~40 mins for 2g)	
C_{max} (Peak Conc.)	Up to 70% higher than oral	Lower and more variable	
AUC (Overall Exposure)	Similar to oral (if oral absorption complete)	Similar to IV (if absorption complete)	
Effect of Morphine on PK	Not impacted	Absorption reduced/delayed (C_{max} ↓, T_{max} ↑, AUC ↓), unpredictable release	
CSF AUC_{0-6} (1g dose)	~24.9 µg·h/mL	~14.2 µg·h/mL	
Initial Liver Exposure	Reduced by ~50% compared to oral	Higher due to first-pass effect	

This table offers a concise side-by-side comparison of the fundamental pharmacokinetic differences, which are crucial for understanding the potential advantages and disadvantages inherent to each route of administration. It consolidates complex pharmacokinetic data from multiple sources into an easily digestible format, directly addressing why one route might perform differently from a pharmacological standpoint. The inclusion of critical factors such as bioavailability, speed of onset (reflected by T_{max} and C_{max}), the significant impact of opioids on oral paracetamol's pharmacokinetics, CSF concentrations, and initial liver exposure highlights parameters with direct clinical relevance for decision-making.

3. Clinical Efficacy: Evidence from Comparative Studies

While pharmacokinetic parameters provide a theoretical basis for potential differences in drug action, clinical efficacy studies are essential to determine how these differences translate into actual patient outcomes. This section evaluates the comparative clinical performance of IV and oral paracetamol in pain management across various settings, focusing on onset and duration of analgesia, efficacy in postoperative and acute pain, and considerations in pediatric populations.

3.1. Onset, Peak, and Duration of Analgesic Effect

A key differentiator often cited for IV paracetamol is its speed of action.

- **Onset of Analgesia:** Intravenous paracetamol, or its prodrug propacetamol, consistently demonstrates a faster onset of analgesia compared to oral formulations. Studies, particularly in the context of postoperative pain such as after third molar surgery, have reported meaningful pain relief with IV propacetamol in as little as 8 minutes, with maximal pain relief achieved by 15 minutes. The time to peak analgesic effect for IV paracetamol is generally reported to be within 10 minutes of administration. In contrast, oral paracetamol exhibits a slower onset; the same studies indicated meaningful pain relief at approximately 37 minutes and maximal pain relief around 1 hour after oral administration. The time to peak analgesic effect for oral paracetamol is correspondingly estimated at about 1 hour. This rapid onset with IV administration is a direct consequence of its pharmacokinetic profile, specifically the swift achievement of T_{max} and high C_{max}, leading to quicker attainment of therapeutic concentrations in both plasma and the CNS. This temporal advantage is a clear instance where a pharmacokinetic difference translates into a tangible, albeit primarily initial, clinical benefit, making IV paracetamol particularly suitable for acute pain situations where rapid relief is paramount.
- **Duration of Action:** Despite differences in onset, the duration of analgesic action for both IV and oral paracetamol appears to be similar, typically lasting around 4 to 6 hours. One meta-analysis also indicated that a single dose of IV paracetamol or propacetamol provides effective analgesia for about 4 hours in a proportion of patients. If the overall duration of analgesia is comparable once therapeutic concentrations are achieved by both routes (assuming similar elimination half-lives and adequate oral absorption), the primary advantage of the IV route is concentrated in the initial phase of treatment. For sustained analgesia beyond the first hour or so, where the initial rapid onset becomes less critical, the routes may perform comparably. This implies that for ongoing pain management, the incremental benefits of continued IV use may diminish over time, bringing the cost-effectiveness of this route into question if oral administration is a viable alternative.

3.2. Efficacy in Postoperative Pain Management

The postoperative setting is a common area for the use of both IV and oral paracetamol, often as part of a multimodal analgesic regimen.

- **Pain Score Reduction:** The evidence regarding comparative reduction in pain scores is mixed. Some systematic reviews suggest that IV paracetamol may offer a small advantage over oral paracetamol premedication, reporting, for example, a 0.5-point lower postoperative pain score on a visual analogue scale (VAS). However, this magnitude of difference (e.g., 0.5 points on a 10-point scale) may be statistically significant but is unlikely to be clinically meaningful for many patients. The concept of Minimal Clinically Important Difference (MCID) for pain scores, often considered to be 1-2 points on a 10-point VAS, should be taken into account. If an observed difference falls below the MCID, the additional cost and complexity of IV paracetamol may not be justified for routine use based on this outcome alone. Conversely, other systematic reviews and direct head-to-head comparison trials have found no significant differences in postoperative pain scores at various time points (e.g., 2, 24, and 48 hours) between IV and oral paracetamol when administered in equivalent doses and with appropriate timing for the oral dose. One

randomized controlled trial (RCT) specifically concluded that there was no clinical benefit of IV paracetamol compared with oral paracetamol when the timing of administration was correctly managed. In specific surgical contexts, such as lumbar disc surgery, IV paracetamol (compared to placebo) has been shown to reduce postoperative pain scores at multiple time points up to 24 hours.

- **Number Needed to Treat (NNT):** Some sources report an NNT for a 50% reduction in postoperative pain (when dosed at 1000 mg every 6 hours) as 5.3 for IV acetaminophen versus 3.8 for oral acetaminophen. It is crucial to interpret this NNT data with caution. These figures are derived from separate Cochrane reviews comparing each formulation against placebo (Tzortzopoulou et al. 2011 for IV propacetamol/paracetamol vs. placebo, and Toms et al. 2008 for oral paracetamol vs. placebo) , not from direct head-to-head comparisons of IV versus oral paracetamol. Therefore, these specific NNTs cannot be used to directly conclude that oral paracetamol is superior to IV paracetamol. NNTs from separate studies comparing different interventions to a common control (placebo) can be influenced by inherent differences in the patient populations, types of surgery, baseline pain intensities, and definitions of pain relief used in the respective underlying trials. A direct head-to-head RCT or a meta-analysis of such RCTs is necessary to truly compare the NNT of IV versus oral paracetamol. Another source provides an NNT of 4.0 (95% CI 3.5 to 4.8) for IV propacetamol/acetaminophen versus placebo for achieving at least 50% pain relief over 4 hours , which is comparable to the NNT reported for oral paracetamol versus placebo.
- **Opioid-Sparing Effects:** IV paracetamol has demonstrated an ability to reduce postoperative opioid consumption in various surgical settings, including joint arthroplasty, abdominal surgery, caesarean delivery, and lumbar disc surgery. The reduction in morphine consumption can be in the range of approximately 20-46%. However, a critical observation is that this reduction in opioid dosage does not always correlate with a clinically significant decrease in opioid-related adverse effects, such as nausea and vomiting. This finding questions the ultimate clinical significance of the opioid reduction itself if patients continue to experience similar rates of side effects. A primary goal of multimodal analgesia, which includes opioid-sparing strategies, is to improve the tolerability of pain management. If this is not achieved despite lower opioid doses, the benefit of the sparing effect is diminished. This could be due to various factors, including the possibility that the remaining opioid dose is still sufficient to cause side effects, paracetamol itself might contribute to some GI symptoms in certain individuals, or the studies were underpowered to detect significant differences in the incidence of adverse events.
- **Time to Rescue Analgesia:** Many studies have found no significant difference in the time to the first request for rescue analgesia between patient groups receiving IV paracetamol and those receiving oral paracetamol.

3.3. Efficacy in Acute Pain (e.g., Emergency Department settings)

In emergency department (ED) settings, where rapid and effective pain relief is often required, the choice of analgesic route is important. A prospective, double-blind, double-dummy, randomized controlled trial involving adult patients with moderate to severe acute pain in the ED found no evidence of superiority for IV paracetamol when compared directly to oral paracetamol. Both formulations achieved a clinically significant mean reduction in pain scores on a Visual Analogue Scale (VAS) at 30 minutes (IV group: 16.0 mm reduction; Oral group: 14.6

mm reduction). The difference between the groups was minimal (-1.4 mm, 95% CI -11.6 to 8.8) and not statistically significant. Furthermore, there were no significant differences in secondary outcomes, including the need for post-intervention intravenous opioid administration (rescue analgesia), patient satisfaction levels, reported side effects, or length of stay in the ED between the two groups. This evidence suggests that for adult ED patients who are capable of taking oral medication, routine preference for IV paracetamol over oral paracetamol for acute pain is not supported, particularly given the similar efficacy and the substantially higher cost associated with the IV route. This challenges the assumption that the faster pharmacokinetic onset of IV paracetamol automatically translates to superior overall pain management in all acute pain scenarios encountered in the ED.

When IV acetaminophen has been compared to IV opioids in the ED, systematic reviews indicate that in most studies there was no significant difference in pain reduction at 30, 60, or 120 minutes, although some individual RCTs did report greater pain reduction with IV opioids. An important finding from these comparisons is that IV acetaminophen was generally associated with fewer adverse events than IV opioids. This positions IV paracetamol as a potentially viable alternative or adjunct within a multimodal analgesic strategy in the ED, offering a better safety profile than opioids, rather than necessarily being a direct replacement for opioids when rapid, potent analgesia is the primary objective for severe pain.

3.4. Considerations in Pediatric Populations

The evidence base comparing IV and oral paracetamol specifically in pediatric populations is less extensive than in adults. A review conducted for the South African National Department of Health indicated uncertainty as to whether IV or rectal paracetamol is superior in terms of reducing pain intensity after surgery in children. This review did note that IV paracetamol is less costly than rectal paracetamol (a finding that may be specific to that healthcare system's procurement) and that rectal administration of paracetamol is associated with highly variable pharmacokinetics. IV paracetamol is generally considered effective and safe for peri-operative analgesia in children of all ages, including newborns.

One systematic review focusing on acute pain in the ED found no primary studies that directly compared IV versus oral acetaminophen in children. Regulatory bodies like the UK's Medicines and Healthcare products Regulatory Agency (MHRA) have issued updated dosing guidelines for paediatric oral paracetamol liquids to ensure optimal dosing based on age and weight, underscoring the importance of accurate dosing in this population. Similarly, Queensland Health in Australia provides detailed dosing guidelines for both oral and IV paracetamol in children, noting that product information for IV paracetamol may suggest lower doses for children weighing 10kg or less, but that higher limits have been used safely in clinical practice.

In pediatric practice, the choice of administration route is often heavily influenced by practical considerations. These include the child's age and ability to swallow oral medications, the availability and acceptability of rectal formulations (which can be distressing for some children and parents), and the critical need for precise dosing. The known pharmacokinetic variability of rectal paracetamol makes the IV route a more predictable alternative when oral administration is not feasible. While IV administration is invasive, it offers the certainty of dose delivery and more predictable pharmacokinetics, which are particularly crucial in vulnerable pediatric patients. The observation from one review that IV paracetamol might be less costly than rectal paracetamol is noteworthy, as it contrasts with the typical cost dynamic seen in adult IV versus oral comparisons. This could be attributable to specific tendering processes or pricing structures for suppositories within that particular healthcare system, highlighting how local economic factors

can influence drug choices.

Table 2: Summary of Comparative Clinical Efficacy in Key Settings

The following table summarizes the comparative clinical efficacy findings:

Setting/Outcome	IV Paracetamol	Oral Paracetamol	Comparative Finding	Key References
Onset of Analgesia	Faster (e.g., 8-15 mins for meaningful/maximal relief with propacetamol/IV)	Slower (e.g., 37-60 mins for meaningful/maximal relief)	IV offers more rapid onset of analgesia.	
Duration of Analgesia	~4-6 hours	~4-6 hours	Similar duration of action for both routes.	
Postoperative Pain	Pain scores: Small reduction (e.g., 0.5 points) vs. oral in some reviews. NNT vs. Placebo: ~4.0-5.3.	NNT vs. Placebo: ~3.8. Pain scores: Similar to IV in many direct comparisons.	Mixed results: Some reviews show minor IV benefit, many show no significant clinical difference if oral is timed correctly. NNT data needs careful interpretation.	
Opioid Sparing (Postop)	Reduces opioid consumption by ~20-46% in some studies.	Less evidence for similar magnitude of sparing compared to IV.	IV paracetamol can reduce opioid use, but this may not always reduce opioid side effects.	
Acute Pain (ED)	Clinically significant pain reduction at 30 mins (e.g., 16.0mm VAS change).	Clinically significant pain reduction at 30 mins (e.g., 14.6mm VAS change).	No superiority of IV over oral in direct RCT for efficacy, side effects, or length of stay.	
Pediatric Postop Pain	Effective and safe; more predictable PK and potentially less costly than rectal in some contexts.	Preferred if child can take oral; dosing guidelines crucial.	IV is a viable alternative when oral/rectal routes are problematic; evidence for direct IV vs. oral superiority is limited.	

This table synthesizes complex clinical trial data across different pain settings, providing a quick comparative overview of efficacy. Clinical efficacy is central to determining if one route "works better." The table breaks down efficacy by key parameters and settings, allowing for rapid

comparison and highlighting areas where evidence is robust, mixed, or lacking. The "Comparative Finding" column offers a nuanced interpretation, reflecting the critical appraisal necessary for such data.

4. Safety and Tolerability Profiles

The safety and tolerability of any medication are critical considerations in clinical practice. Paracetamol is generally regarded as a safe drug when used at recommended therapeutic doses, but differences in administration route could potentially influence its safety profile.

4.1. Comparative Incidence and Nature of Adverse Events

At therapeutic doses, paracetamol typically has a favorable adverse drug reaction profile. Direct comparative studies have generally not found significant differences in the incidence of common systemic adverse events between IV and oral paracetamol. For instance, the ED-based RCT comparing IV and oral paracetamol for acute pain reported that side effects did not differ significantly between the two groups. Similarly, a systematic review found no notable difference in the occurrence of analgesia-related adverse events such as vomiting/nausea or pruritus between patients receiving IV and oral paracetamol. When IV paracetamol was used as an adjunct for pain management after lumbar disc surgery, there were no differences in postoperative adverse effects compared to placebo groups.

Common adverse events listed for IV acetaminophen (Ofirmev) include nausea, vomiting, headache, and constipation. Oral administration of paracetamol can also be associated with these, and rarely, with skin rash, hypersensitivity reactions, nephrotoxicity (characterized by elevations in blood urea nitrogen and creatinine), and hematological abnormalities such as anemia, leukopenia, neutropenia, and pancytopenia. The available evidence suggests that when administered correctly and at appropriate therapeutic doses, both IV and oral paracetamol exhibit comparable systemic adverse event profiles with respect to common, short-term side effects. The choice of administration route does not appear to significantly alter the likelihood of typical paracetamol-related systemic side effects, such as nausea, if the overall drug exposure (AUC) is similar.

4.2. Hepatotoxicity Risk: Influence of Administration Route and First-Pass Metabolism

The most significant dose-related toxicity of paracetamol is hepatotoxicity, which can occur in cases of overdose and is mediated by its toxic metabolite, NAPQI. As discussed earlier, IV acetaminophen bypasses first-pass hepatic metabolism, which means the liver is exposed to approximately 50% less initial paracetamol compared to an equivalent oral dose. This pharmacokinetic difference has led to the theory that IV administration might carry a lower risk of hepatotoxicity.

The theoretical risk of hepatotoxicity with IV acetaminophen is generally considered to be low when the drug is dosed correctly. Incidents of hepatotoxicity associated with IV paracetamol have been primarily attributed to dosing errors, particularly exceeding the maximum recommended daily dose, and this risk can be potentiated by factors such as malnutrition. While the reduced initial liver exposure with IV paracetamol is a theoretical advantage for hepatoprotection, there is currently insufficient clinical evidence to suggest a meaningful

difference in the risk of hepatotoxicity between correctly dosed IV and oral paracetamol in patients with normal liver function. The primary driver of paracetamol-induced hepatotoxicity remains the overall dose administered and individual patient susceptibility factors. If the total daily dose (from all routes of administration) is the main determinant of risk, and the AUCs are similar between IV and well-absorbed oral paracetamol, the impact of the administration route on hepatotoxicity at therapeutic levels might be minimal unless the first-pass effect with oral administration significantly stresses hepatic metabolic pathways in particularly susceptible individuals.
It is also worth considering that the potential for dosing errors might, in some circumstances, be higher with IV formulations compared to the simpler administration of oral tablets. IV administration involves multiple steps, including calculations for weight-based dosing (especially critical in pediatric patients), drug preparation (e.g., drawing up, potential dilution), and the setup and monitoring of infusion devices. These procedural complexities could inadvertently increase the risk of errors if not managed with meticulous care.
One review noted that transient elevation of liver enzymes was reported more frequently with repeated paracetamol administration (route not always specified, but often implied to be oral in the context of chronic use) in patients with spinal pain when compared to placebo. This suggests that liver function monitoring might be prudent with prolonged, regular use of paracetamol, irrespective of the route.

4.3. Specific Risks Associated with Intravenous Administration

Beyond systemic effects, IV administration carries inherent risks that are not associated with the oral route. These include the potential for infection at the injection site, phlebitis (inflammation of a vein), and local tissue irritation or extravasation injuries. Additionally, IV paracetamol requires administration by a healthcare professional and typically involves a 15-minute infusion period, which is more time-consuming and resource-intensive than taking an oral tablet. These IV-specific risks, although generally low in incidence, contribute to the overall burden of IV therapy and must be factored into any risk-benefit assessment, particularly when oral administration is a viable and equally effective alternative. These are tangible downsides that can offset some of the perceived convenience or pharmacokinetic advantages of IV therapy in certain situations.

5. Clinical Utility and Practical Considerations

Beyond direct pharmacological actions and clinical efficacy in trials, the practical utility of a drug formulation is determined by a range of factors including patient-specific conditions, ease of administration, cost, and broader healthcare system implications.

5.1. Situations Favoring Intravenous Administration

Intravenous paracetamol has a clear and undisputed role in specific clinical scenarios:

- **When oral administration is not possible or suitable:** This is perhaps the most straightforward indication. IV paracetamol is essential for patients who are nil by mouth (NPO), actively vomiting, have an impaired ability to swallow, or possess conditions that preclude oral intake.
- **Impaired gastrointestinal (GI) function:** In patients with conditions like postoperative

ileus, malabsorption syndromes, or other significant GI dysfunctions where the absorption of oral medications is likely to be compromised or unpredictable, IV paracetamol offers a reliable route of administration.
- **Need for rapid onset of analgesia:** In settings where a very quick onset of pain relief is critical, such as in some acute trauma situations or immediately postoperatively, the faster T_{max} of IV paracetamol can be advantageous.
- **Predictable plasma concentrations are essential:** Particularly when oral absorption may be compromised by factors like co-administration with opioids (which delay gastric emptying), IV paracetamol provides more predictable and consistent plasma concentrations, ensuring reliable drug delivery.
- **Specific vulnerable populations:** Empirically, some experts suggest IV paracetamol may have a role in managing fever and pain in imminently dying patients who cannot swallow, especially if the rectal route is not preferred or is contraindicated (e.g., in neutropenic patients or those who have undergone colectomy).
- **When alternatives are undesirable:** IV paracetamol can be a useful option when other analgesics like NSAIDs or opioids are contraindicated or their use needs to be minimized due to patient-specific risks or comorbidities.

The primary utility of IV paracetamol appears to lie in its capacity as an enabler of paracetamol therapy in situations where the oral route is either contraindicated or demonstrably unreliable, rather than it being a universally superior analgesic formulation. It effectively fills a niche for specific patient needs, ensuring that these individuals can still receive the benefits of paracetamol. In these contexts, its "superiority" is often one of access and reliability of drug delivery, not necessarily intrinsic analgesic potency over a well-absorbed oral dose.

5.2. Situations Where Oral Administration is Preferred or Non-Inferior

Oral paracetamol remains the preferred or non-inferior option in many common clinical situations:

- **Whenever feasible and GI function is normal:** If a patient can take oral medications and has no conditions impairing GI absorption, the oral route is generally the first choice.
- **Routine pain management:** For most cases of mild to moderate pain where an extremely rapid onset is not the overriding priority, and where cost is a consideration, oral paracetamol is appropriate.
- **Emergency Department settings:** As demonstrated by RCT evidence, in adult ED patients with acute pain who can take oral medication, IV paracetamol has not shown clinical superiority over oral paracetamol.
- **Postoperative settings with appropriate timing:** When oral paracetamol is administered as a premedication with adequate timing to allow for absorption, it can provide postoperative analgesia that is non-inferior to IV paracetamol.

Given the significantly lower cost and comparable efficacy in many common scenarios for patients who can utilize the oral route, oral paracetamol should remain the default first-line option. The over-utilization of IV paracetamol in situations where oral administration is appropriate represents suboptimal stewardship of healthcare resources.

5.3. Cost-Effectiveness and Economic Implications

The economic disparity between IV and oral paracetamol is substantial and a major factor in clinical decision-making. IV acetaminophen is reported to cost significantly more than an

equivalent dose of oral acetaminophen – with figures cited as being more than 20 times, 10-30 times, or even 26 times more expensive. One audit highlighted a cost of £9412 per 100 patients for IV paracetamol compared to just £18.5 for oral paracetamol for the same number of patients. This considerable cost difference raises significant controversy regarding whether IV acetaminophen is a cost-effective analgesic, particularly in light of evidence that often fails to demonstrate clear clinical superiority over the oral route. One review specifically noted that no studies on the cost-effectiveness of IV versus oral acetaminophen in the ED setting were found. The economic argument against the routine use of IV paracetamol is therefore very strong. The substantial cost differential necessitates a high degree of proven, clinically meaningful benefit to justify the selection of IV paracetamol when oral administration is a viable option. The current body of evidence largely does not support such widespread superior benefit that would routinely justify the additional expense.

Audits and institutional initiatives have demonstrated that significant cost savings can be achieved by adhering to guidelines that promote the preferential use of oral paracetamol and by facilitating a timely switch from IV to oral formulations once a patient's clinical condition allows (e.g., once an oral diet is resumed postoperatively). Such measures have been shown to lead to considerable cost reductions, for example, an almost 50% cost reduction in one reported audit cycle. These findings underscore the financial impact of prescribing habits and highlight the potential for relatively simple interventions, such as prompts on automated pharmacy dispensing units , to improve resource allocation and promote more cost-effective practices. This suggests that current IV paracetamol use may frequently extend beyond strictly indicated scenarios, potentially driven by factors such as perceived convenience, assumptions of superiority that are not always evidence-based, or a lack of strict adherence to prescribing guidelines.

5.4. Environmental Impact of Different Formulations

An increasingly recognized, though often historically overlooked, aspect of therapeutic choice is the environmental impact of medications and their delivery systems. Oral paracetamol has a considerably smaller environmental footprint compared to its intravenous counterpart. It is estimated that oral paracetamol releases approximately eight times less carbon dioxide (CO_2) per dose than IV paracetamol. To put this into perspective, each dose of IV paracetamol is reported to generate an amount of CO_2 equivalent to that produced in the manufacture of eight plastic bottles.

The use of IV paracetamol also contributes to a greater volume of clinical waste, primarily due to the IV line packaging, empty infusion bottles or bags, and associated administration sets, which are typically disposed of after each dose. In contrast, oral paracetamol often comes in multi-dose blister packs with significantly less associated waste. Efforts to switch from IV to oral paracetamol where appropriate have been shown to lead to tangible reductions in plastic waste (e.g., a potential 400kg reduction per year in one hospital) and carbon equivalent savings (e.g., 700kg CO_2 equivalent per year). The significantly larger carbon footprint and greater plastic waste associated with IV paracetamol add another important dimension to the argument for preferring oral administration when it is clinically appropriate and equally effective. Choosing less resource-intensive options, when clinically equivalent, aligns with the growing principles of sustainable healthcare and environmental responsibility within medical practice.

6. Guidance from Professional Bodies and Health

Authorities

Recommendations from professional organizations and health authorities play a crucial role in guiding clinical practice and formulary decisions. Several bodies have provided perspectives on the use of IV versus oral paracetamol.

- **National Institute for Health and Care Excellence (NICE, UK):** NICE guidelines (specifically NG180) clearly recommend not to offer intravenous paracetamol unless the individual is unable to take oral medicine. Audits assessing adherence to this guideline have indicated that improvements are possible and that such improvements can lead to substantial cost savings and potentially better patient outcomes, such as earlier mobilization post-surgery.
- **American Society of Anesthesiologists (ASA):** While no single, recent overarching ASA guideline (2022-2024) specifically dedicated to IV versus oral paracetamol route selection for general pain management was identified in the provided materials beyond updates to preoperative fasting guidelines , historical ASA guidelines and related literature have suggested that there is often inadequate differentiation in efficacy between IV and oral paracetamol to consistently warrant the higher acquisition cost and longer administration time associated with the IV formulation. More recent content from StatPearls (updated January 2024), which often reflects common understanding and evidence synthesis relevant to US practice, notes a literature review by Tompkins et al. that found a lack of evidence supporting the efficacy of IV acetaminophen over oral or rectal routes for postoperative pain control, concluding that IV paracetamol offers limited clinical benefits in this context. This resource emphasizes selecting appropriate acetaminophen formulations based on individual patient needs (such as age, weight, and ability to swallow) and consistently considering all routes of administration when calculating the maximum daily dosage to avoid toxicity.
- **Hospital-Level Guidance (e.g., University Hospital Southampton, Aneurin Bevan University Health Board):** Individual hospitals and health boards often develop local policies. For example, University Hospital Southampton advocates for the use of oral paracetamol over IV paracetamol, citing equal efficacy, significantly lower cost, and a reduced environmental impact. An audit at this institution found that in 40% of cases where IV paracetamol was administered, oral paracetamol could have been used instead. Similarly, initiatives at Aneurin Bevan University Health Board to reduce IV paracetamol use where oral is appropriate have highlighted cost savings, plastic waste reduction, and carbon footprint reduction, alongside increased patient safety.
- **European Medicines Agency (EMA):** The provided information related to the EMA primarily focuses on bioequivalence guidance for oral immediate-release paracetamol formulations and updated dosing for pediatric oral liquid paracetamol. These documents do not offer a direct comparative guideline on the selection of IV versus oral routes based on efficacy for general pain management.
- **Queensland Health (Australia):** This health authority provides comprehensive guidelines for the safe use of paracetamol, including specific dosing recommendations for both oral and IV routes in adult and pediatric populations. The guidelines also detail conditions where dose adjustments are necessary and note that while product information for IV paracetamol in children weighing 10kg or less may suggest lower doses, higher limits have been used safely in clinical practice under appropriate supervision.

There appears to be a general consensus among guiding bodies and in health economic

evaluations that oral paracetamol should be the preferred route of administration if the patient is able to take it and has normal GI function. This preference is primarily driven by the substantially lower cost of oral formulations and the lack of consistent, compelling evidence demonstrating superior clinical efficacy of IV paracetamol in routine situations that would justify its expense and additional resource requirements. Despite these guidelines and the supporting evidence, a gap often exists in clinical adherence, with IV paracetamol sometimes being used even when oral administration is feasible. This discrepancy suggests that factors beyond evidence and formal guidelines—such as perceived convenience by staff, physician habit, patient expectations, or historical marketing influences—might be contributing to prescribing practices that are not always aligned with optimal resource stewardship.

Table 3: Overview of Guideline Recommendations and Cost/Environmental Considerations

Aspect	Intravenous (IV) Paracetamol	Oral Paracetamol	Key Guidance/References
NICE Recommendation	Not recommended if oral route is possible.	Preferred route if patient can take oral medicine.	
ASA (General Sentiment)	Higher cost/administration time may not be warranted due to inadequate differentiation from oral. Limited clinical benefit over oral/rectal in post-op pain.	Select based on patient needs; often the default if feasible.	
Cost	Significantly more expensive (10-30x oral, e.g., £9412 vs £18.5 per 100 patients).	Highly cost-effective.	
Environmental Impact	Higher carbon footprint (~8x oral), more plastic waste.	Lower carbon footprint, less plastic waste.	
Situational Use	Indicated when oral route impossible/unreliable (NPO, GI dysfunction, opioid co-admin for PK reliability), or very rapid onset critical.	Preferred for routine pain management if patient can take oral and GI function is normal.	

This table provides a crucial summary of practical and authoritative guidance influencing the choice between IV and oral paracetamol. Clinicians rely on guidelines from professional bodies, and cost and environmental impact are increasingly important practical considerations in healthcare. The table distills key recommendations and data points related to these non-efficacy/safety factors, which heavily influence real-world decision-making, reinforcing the message that the "best" route is often determined by context and practicalities, not just

pharmacology alone.

7. Synthesis and Clinical Recommendations

The question of whether intravenous (IV) paracetamol "works better" than oral paracetamol requires a nuanced answer, integrating evidence from pharmacological studies, clinical trials, safety assessments, and practical considerations such as cost and environmental impact.

7.1. Does IV Paracetamol Work "Better" Than Oral Paracetamol? A Nuanced Answer.

From a purely **pharmacokinetic perspective**, IV paracetamol exhibits several advantages: it offers 100% bioavailability, achieves a faster time to peak plasma concentration (T_{max}) and a higher peak plasma concentration (C_{max}), bypasses first-pass hepatic metabolism (potentially reducing the initial metabolic load on the liver), and results in higher cerebrospinal fluid (CSF) concentrations more rapidly than oral formulations. Critically, its pharmacokinetic profile is more predictable and is not adversely affected by the co-administration of opioids, a common scenario in postoperative care where oral paracetamol absorption can be significantly impaired and unreliable.
However, whether these pharmacokinetic advantages consistently translate into **clinically superior outcomes** is context-dependent:

- **Faster Onset of Analgesia:** IV paracetamol does provide a demonstrably faster onset of analgesia. This is a clear clinical benefit in acute situations where rapid pain relief is a priority.
- **Essential When Oral Route is Impaired:** IV paracetamol is undeniably "better" and, indeed, essential when patients cannot take oral medications (e.g., NPO status, vomiting) or when gastrointestinal absorption is compromised (e.g., ileus, malabsorption syndromes). In these cases, it ensures that patients receive the therapeutic benefits of paracetamol.
- **Reliability with Opioid Co-administration:** In the context of concurrent opioid use, which is common in postoperative pain management, the predictable pharmacokinetics of IV paracetamol make it a more reliable option for achieving consistent therapeutic paracetamol levels compared to oral administration.
- **Often Not Clinically Superior in General Efficacy:** For overall magnitude and duration of pain relief, multiple systematic reviews and RCTs suggest that IV paracetamol is frequently not clinically superior to appropriately administered oral paracetamol in patients who can effectively take and absorb oral medication. Small, statistically significant differences in pain scores reported in some studies may not always translate to clinically meaningful improvements for patients. The NNT data sometimes cited (e.g., IV NNT 5.3 vs. oral NNT 3.8) requires careful interpretation, as these figures are typically derived from separate placebo-controlled meta-analyses rather than direct head-to-head comparisons, and thus cannot be used to definitively conclude oral superiority over IV.
- **Safety Profile:** The systemic adverse event profiles of IV and oral paracetamol are generally similar when administered at correct therapeutic doses. IV administration carries specific site-related risks (e.g., phlebitis, infection). The theoretical benefit of reduced initial liver exposure with IV paracetamol has not yet been conclusively proven to translate into clinically significant differences in hepatotoxicity risk at correct therapeutic doses in

patients with normal liver function; dosing errors remain the primary concern for IV paracetamol-related hepatotoxicity.
- **Cost and Environmental Impact:** Oral paracetamol is vastly superior to IV paracetamol in terms of cost-effectiveness and has a significantly lower environmental impact.

In synthesis, "better" is contingent upon the specific metric of evaluation and the clinical context. IV paracetamol offers distinct pharmacokinetic advantages and is indispensable in certain clinical situations (e.g., NPO patients, impaired GI absorption, need for absolute reliability with opioid co-administration). However, these advantages do not consistently translate into superior overall analgesic efficacy or safety for the majority of patients who can effectively use the oral route. The increased utilization and marketing of IV paracetamol may, in some instances, have outpaced robust evidence demonstrating its general clinical superiority over the more economical and environmentally friendly oral formulation.

7.2. Evidence-Based Recommendations for Route Selection

Based on the comprehensive analysis of the available evidence, the following recommendations for route selection are proposed:

1. **Oral paracetamol should be the first-line choice** for the management of mild to moderate pain and for fever reduction in patients who are able to take oral medications and have normal gastrointestinal absorption. This recommendation is based on its comparable efficacy to IV paracetamol in many common clinical settings, its well-established safety profile at therapeutic doses, and its significant advantages in terms of cost-effectiveness and lower environmental impact.
2. **Intravenous (IV) paracetamol is recommended and offers clear advantages in the following specific situations:**
    - For patients who are **nil per os (NPO)** or have **contraindications to oral administration** (e.g., active vomiting, inability to swallow, pharyngeal or esophageal obstruction).
    - For patients with **significant gastrointestinal dysfunction** where oral absorption is likely to be impaired, unpredictable, or delayed (e.g., postoperative ileus, short bowel syndrome, malabsorption disorders, or during episodes of severe nausea/vomiting that preclude oral intake).
    - In the **immediate perioperative period, particularly when opioids are being co-administered**, to ensure reliable and predictable achievement of therapeutic paracetamol plasma concentrations, thereby optimizing its contribution to multimodal analgesia.
    - When a **very rapid onset of analgesia (i.e., within 10-15 minutes) is critically important** for patient comfort and management, and the anticipated benefits are deemed to outweigh the additional costs and potential risks associated with IV administration.
    - As a component of a **multimodal analgesic regimen** in situations where ensuring 100% bioavailability and predictable plasma levels of paracetamol is considered essential for the overall analgesic strategy.
3. **Transition from IV to Oral Paracetamol:** Patients who are initiated on IV paracetamol should be reassessed regularly, and a transition to an appropriate oral formulation should be made as soon as clinically appropriate (i.e., once they can reliably tolerate oral intake and there is no significant concern about GI absorption). This practice helps to reduce healthcare costs, minimize risks associated with IV therapy, and lessen the environmental

impact.

4. **Dosing and Monitoring:** Regardless of the route of administration, it is imperative to ensure appropriate dosing, including weight-based calculations where necessary (particularly in pediatric patients and low-weight adults). Adherence to maximum recommended daily dose limits from all sources of paracetamol (including combination products) is crucial to minimize the risk of hepatotoxicity.
5. **Consideration of Local Guidelines and Formulary Policies:** Clinicians should be aware of and take into account local institutional guidelines, formulary restrictions, and health system policies, which often promote the preferential use of oral paracetamol based on evidence of comparable efficacy in many settings and significant cost-effectiveness advantages.

A "step-up" or "step-down" approach to paracetamol administration is rational: begin with oral paracetamol if feasible. Utilize IV paracetamol if specific clinical criteria necessitate this route. Transition back to oral paracetamol as soon as the patient's condition permits. This approach effectively balances the need for effective analgesia with crucial considerations of patient safety, cost containment, and responsible resource stewardship.

Future research should continue to focus on well-designed, head-to-head comparative trials in specific, clearly defined patient populations where the benefits of IV paracetamol are most plausible (e.g., particular types of surgery associated with high opioid requirements or significant postoperative GI dysfunction, or patients with documented malabsorption syndromes). Such studies should include robust patient-reported outcomes, functional recovery metrics, and comprehensive cost-effectiveness analyses. There also remains a need for more direct comparative studies of IV versus oral paracetamol formulations in pediatric populations to further refine evidence-based recommendations for this group.

Works cited

1. resources.wfsahq.org, https://resources.wfsahq.org/wp-content/uploads/uia23-Paracetam-ol-a-review-of-three-routes-of-administrati-on.pdf 2. FF #302 Oral vs Intravenous Acetaminophen | Palliative Care ..., https://www.mypcnow.org/fast-fact/oral-vs-intravenous-acetaminophen/ 3. The efficacy and safety of paracetamol for pain relief: an overview of systematic reviews, https://www.mja.com.au/journal/2021/214/7/efficacy-and-safety-paracetamol-pain-relief-overview-systematic-reviews 4. Intravenous versus Oral Acetaminophen for Pain: Systematic ..., https://pmc.ncbi.nlm.nih.gov/articles/PMC4485512/ 5. Clinical Overview - GOV.UK, https://assets.publishing.service.gov.uk/media/659e6193915e0b000d5838b1/FOI_22-1115_PDF_attachment__2_.pdf 6. Mechanism of action of paracetamol - PubMed, https://pubmed.ncbi.nlm.nih.gov/15662292/ 7. Paracetamol (Acetaminophen): mechanisms of action - PubMed, https://pubmed.ncbi.nlm.nih.gov/18811827/ 8. Effect of Intravenous Paracetamol on Opioid Consumption in Multimodal Analgesia After Lumbar Disc Surgery: A Meta-Analysis of Randomized Controlled Trials - Frontiers, https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2022.860106/full 9. FF #302 Oral vs Intravenous Acetaminophen - Palliative Care Network of Wisconsin, https://www.mypcnow.org/fast-fact/oral-vs-intravenous-acetaminophen/?print=print 10. What is the comparative efficacy of intravenous (IV) versus oral acetaminophen (paracetamol) for pain management? - Dr.Oracle AI, https://www.droracle.ai/articles/41027/intravenous-vs-oral 11. Pharmacokinetics of Oral and Intravenous Paracetamol (Acetaminophen) When Co-Administered with Intravenous Morphine in Healthy Adult Subjects - PubMed Central,

https://pmc.ncbi.nlm.nih.gov/articles/PMC5834589/ 12. AcetaminophenInjectionOFIRME... - VA Pharmacy Benefits Management, https://www.pbm.va.gov/clinicalguidance/abbreviatedreviews/AcetaminophenInjectionOFIRMEVAbbreviatedReview.doc 13. Acetaminophen - StatPearls - NCBI Bookshelf, https://www.ncbi.nlm.nih.gov/books/NBK482369/ 14. Intravenous versus oral paracetamol for postoperative analgesia: A ..., https://www.researchgate.net/publication/347790300_Intravenous_versus_oral_paracetamol_for_postoperative_analgesia_A_systematic_review 15. Intravenous versus oral paracetamol for acute pain in adults in the emergency department setting: a prospective, double-blind, double-dummy, randomised controlled trial - PubMed, https://pubmed.ncbi.nlm.nih.gov/29247042/ 16. Review: single dose, oral paracetamol reduces moderate to severe postoperative pain, https://ebn.bmj.com/content/7/3/84 17. Intravenous versus oral paracetamol for postoperative analgesia: A systematic review, https://pubmed.ncbi.nlm.nih.gov/33345698/ 18. Effectiveness of oral vs intravenous acetaminophen on pain management following total joint arthroplasty: A systematic review and meta-analysis, https://www.wjgnet.com/2218-5836/full/v16/i4/104452.htm 19. Oral vs intravenous paracetamol for lower third molar extractions under general anaesthesia: is oral administration inferior? | BJA - Oxford Academic, https://academic.oup.com/bja/article/110/3/432/249084 20. Effect of Intravenous Paracetamol on Opioid Consumption in Multimodal Analgesia After Lumbar Disc Surgery: A Meta-Analysis of Randomized Controlled Trials - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC9168366/ 21. Intravenous versus Oral Acetaminophen for Pain: Systematic Review of Current Evidence to Support Clinical Decision-Making - SciSpace, https://scispace.com/pdf/intravenous-versus-oral-acetaminophen-for-pain-systematic-1vlh0de0xm.pdf 22. IV Acetaminophen for Acute Pain in Emergency Departments - NCBI ..., https://www.ncbi.nlm.nih.gov/books/NBK598217/ 23. South African National Department of Health Review Report Component: Treatment of Peri-operative Pain in Children TITLE: Intra, https://www.health.gov.za/wp-content/uploads/2025/05/Intravenous-Paracetamol-for-the-Treatment-of-Post-Operative-Pain-in-Children-June-2022.pdf 24. Paracetamol: updated dosing for children to be introduced - GOV.UK, https://www.gov.uk/drug-safety-update/paracetamol-updated-dosing-for-children-to-be-introduced 25. Guideline for Safe Paracetamol Use - January 2023 - Queensland Health, https://www.health.qld.gov.au/__data/assets/pdf_file/0016/1211443/guideline-safe-paracetamol-use.pdf 26. Emergency department - oral paracetamol vs intravenous ..., https://www.uhs.nhs.uk/departments/emergency-medicine/emergency-department/oral-paracetamol-vs-intravenous-paracetamol-for-pain-relief 27. ThP5.14 - Assessing Adherence and Cost Implications of NICE ..., https://academic.oup.com/bjs/article-pdf/111/Supplement_8/znae197.287/59050331/znae197.287.pdf 28. Award winning, revolutionary paracetamol practice with environmental saving of 700kg CO2 equivalent - Aneurin Bevan University Health Board, https://abuhb.nhs.wales/news/news/award-winning-revolutionary-paracetamol-practice-with-environmental-saving-of-700kg-co2-equivalent/ 29. 2023 Guideline for the Management of Patients With Aneurysmal Subarachnoid Hemorrhage - American Heart Association Journals, https://www.ahajournals.org/doi/10.1161/STR.0000000000000436 30. Carbohydrate-containing Clear Liquids with or without Protein, Chewing Gum, and Pediatric Fasting Duration-A Modular Update of the 2017 American Society of Anesthesiologists Practice Guidelines for Preoperative Fasting - PubMed, https://pubmed.ncbi.nlm.nih.gov/36629465/ 31. Paracetamol oral use

immediate release formulations product-specific bioequivalence guidance - rev.1 - EMA, https://www.ema.europa.eu/en/documents/scientific-guideline/paracetamol-oral-use-immediate-release-formulations-product-specific-bioequivalence-guidance_en.pdf